



## Complete Summary

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### GUIDELINE TITLE

Antithrombotic therapy in neonates and children. American College of Chest Physicians evidence-based clinical practice guidelines (8th edition).

### BIBLIOGRAPHIC SOURCE(S)

Monagle P, Chalmers E, Chan A, DeVeber G, Kirkham F, Massicotte P, Michelson AD. Antithrombotic therapy in neonates and children: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008 Jun;133(6 Suppl):887S-968S. [561 references] [PubMed](#)

### GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Monagle P, Chan A, Massicotte P, Chalmers E, Michelson AD. Antithrombotic therapy in children: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004 Sep;126(3 Suppl):645S-87S.

### \*\* REGULATORY ALERT \*\*

### FDA WARNING/REGULATORY ALERT

**Note from the National Guideline Clearinghouse:** This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- [February 28, 2008, Heparin Sodium Injection](#): The U.S. Food and Drug Administration (FDA) informed the public that Baxter Healthcare Corporation has voluntarily recalled all of their multi-dose and single-use vials of heparin sodium for injection and their heparin lock flush solutions. Alternate heparin manufacturers are expected to be able to increase heparin production sufficiently to supply the U.S. market. There have been reports of serious adverse events including allergic or hypersensitivity-type reactions, with symptoms of oral swelling, nausea, vomiting, sweating, shortness of breath, and cases of severe hypotension.

### COMPLETE SUMMARY CONTENT

\*\* REGULATORY ALERT \*\*

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INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT  
CATEGORIES  
IDENTIFYING INFORMATION AND AVAILABILITY  
DISCLAIMER

## SCOPE

### **DISEASE/CONDITION(S)**

Thrombosis in neonates and children

### **GUIDELINE CATEGORY**

Prevention  
Treatment

### **CLINICAL SPECIALTY**

Cardiology  
Critical Care  
Emergency Medicine  
Family Practice  
Hematology  
Internal Medicine  
Neurology  
Pediatrics

### **INTENDED USERS**

Advanced Practice Nurses  
Allied Health Personnel  
Health Care Providers  
Nurses  
Patients  
Physicians  
Psychologists/Non-physician Behavioral Health Clinicians  
Social Workers

### **GUIDELINE OBJECTIVE(S)**

To provide evidence-based guidelines on the treatment of neonates and children with thrombosis

### **TARGET POPULATION**

Neonates and children with thrombosis

## **INTERVENTIONS AND PRACTICES CONSIDERED**

1. Vitamin K antagonists (VKA)
2. Unfractionated heparin (UFH)
3. Low molecular weight heparin (LMWH) therapy
4. Aspirin
5. Dipyridamole
6. Clopidogrel
7. Monitoring
  - Anti-factor Xa assay
  - Activated partial thromboplastin time (aPTT)
  - International normalized ratio (INR)
  - Duration of anticoagulation therapy
  - Radiological (for children with cerebral sinovenous thrombosis [CSVT])
8. Thrombolysis (urokinase, tissue plasminogen activator [tPA])
9. Plasminogen (fresh frozen plasma)
10. Thrombectomy
11. Surgical intervention
12. Inferior vena cava filter placement
13. Umbilical artery catheter placement
14. Intravenous (IV) gamma globulin, warfarin (for children with Kawasaki's disease)
15. IV hydration, exchange transfusion and long-term transfusion program (in children with sickle cell disease)
16. Revascularization (for children with moyamoya)
17. Fresh frozen plasma, protein C concentrate, liver transplantation (for protein C deficiency)
18. Supportive care

## **MAJOR OUTCOMES CONSIDERED**

- Mortality
- Incidence of thrombosis
- Recurrent thromboembolism
- Incidence of major and minor hemorrhage

## **METHODOLOGY**

### **METHODS USED TO COLLECT/SELECT EVIDENCE**

Hand-searches of Published Literature (Primary Sources)  
Searches of Electronic Databases

### **DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE**

#### **Process of Searching for Evidence**

Defining the clinical question provided the framework for formulating eligibility criteria that guided the search for relevant evidence. In specifying eligibility criteria, authors identified not only patients, interventions, and outcomes, but also methodologic criteria.

For many questions, randomized trials were nonexistent or did not provide sufficient data, and chapter authors included observational studies.

### **Identifying the Evidence**

To identify the relevant evidence, a team of librarians and research associates at the McMaster University Evidence based practice center (EPC) conducted comprehensive literature searches. Methodologic experts (including the editors) and the EPC librarians reviewed each question to ensure the development of a comprehensive search strategy. For example, for questions about antiplatelet agents, the EPC consulted chapter authors to ensure that the search included all relevant antiplatelet agents. More specifically, authors then decided whether to include dipyridamole in a search that already included aspirin, clopidogrel, and ticlopidine.

For each question the authors provided, the librarians searched the Cochrane Database of Systematic Reviews, MEDLINE, and Embase for published English-language literature and human studies between 2002 and May 2006. To filter MEDLINE and Embase search results for RCT evidence, the librarians used the search strategy developed by the Cochrane Collaboration. These searches updated the more comprehensive and sensitive searches conducted for the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy: Evidence Based Guidelines.

The EPC team conducted separate searches for systematic reviews; RCTs; and, if applicable, observational studies. For observational studies, searches were not restricted in terms of methodology. Although increasing the probability of identifying all published studies, this sensitive approach resulted in large numbers of citations for many of the defined clinical questions. Therefore, trained research assistants screened the citation list developed from the search using criteria of increased specificity to reduce the number of irrelevant citations that the authors received. These irrelevant citations included press news, editorials, narrative reviews, single-case reports, studies that included fewer participants than specified by authors as an inclusion criterion, animal studies (any nonhuman studies), and letters to the editor. Authors did not include data from abstracts of meetings for the development of recommendations, and the guideline developers did not explicitly use Internet sources to search for research data. Authors were encouraged, however, to mention abstracts that reported on groundbreaking data that were particularly relevant to a specific question in the chapters in order to alert readers that new, fully published evidence might become available shortly.

### *Standard Consideration of Study Quality*

High-quality clinical guidelines should pay careful attention to the methodologic quality of the studies that form the basis of their recommendations. Using the example of the prevention of venous thromboembolism during air travel, Table 1 in the methodology companion (see "Availability of Companion Documents" field) shows the criteria for assessment of study quality (randomization, concealment or treatment allocation, blinding, completeness of follow-up, and whether the analysis was performed according to the intention-to-treat principle), and Table 2 in the methodology companion (see "Availability of Companion Documents" field) shows the presentation of results that were circulated to the authors. Whereas all

authors attended to these criteria, the guideline developers have summarized the results of the quality assessment for only a minority of the recommendations. Readers can find these summaries in an online appendix to the recommendations (see online supplemental data).

In assessing the quality of observational studies, the guideline developers did not make a distinction between prospective and retrospective because the key issues are unbiased sampling, high-quality measurement of patient characteristics and outcomes, and complete follow-up.

Although it is more likely that these quality criteria will be achieved in prospective studies, prospective studies may fail to achieve them, and retrospective studies may succeed. The guideline developers did make a key distinction about whether internal comparisons exist and their nature. Studies without internal comparisons received the label "case series" unless they met the following criteria: (1) a protocol existed before the date of commencement of data collection; (2) a definition of inclusion and exclusion criteria was available; (3) the study reported the number of excluded patients; (4) the study conducted a standardized follow-up, including description of schedule of follow-up, investigation of suspected outcomes, and criteria used to define outcomes; and (5) the study reported all losses to follow-up.

The guideline developers labeled studies that met these criteria "cohort studies without internal controls." Studies with internal comparisons received the label "cohort studies with concurrent controls" or "cohort studies with historical controls." These cohort studies may succeed or fail to ensure settings, similar time frames, adjustment for differences in patients' characteristics, and follow-up with patients. These features were captured in descriptive tables provided to authors when requested from the EPC.

## **NUMBER OF SOURCE DOCUMENTS**

Not stated

## **METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE**

Weighting According to a Rating Scheme (Scheme Given)

## **RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE**

The rating scheme framework captures the trade-off between benefits and risks (1 or 2) and the methodological quality of the underlying evidence (A, B, or C). See "Grades of recommendations for antithrombotic agents" in the "Availability of Companion Documents" field and the "Rating Scheme for the Strength of the Recommendations." field.

## **METHODS USED TO ANALYZE THE EVIDENCE**

Review of Published Meta-Analyses  
Systematic Review with Evidence Tables

## **DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE**

### **Summarizing Evidence**

The electronic searches also included searches for systematic reviews. If authors were satisfied with a recent high-quality systematic review, evidence from that review provided a foundation for the relevant recommendation.

## **METHODS USED TO FORMULATE THE RECOMMENDATIONS**

Expert Consensus (Consensus Development Conference)

## **DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS**

### **Group-Specific Recommendations**

In general, the guideline developers have endeavored to make their recommendations as specific as possible for patient subgroups differing according to risk. Whenever valid prognostic data were available, the guideline developers used them to estimate absolute effects and made recommendations accordingly. Unfortunately, reliable prognostic indexes are not usually available, limiting the extent to which such group-specific recommendations are possible.

### **Acknowledge Values and Preferences and Resource Use Underlying Recommendations**

Under ideal circumstances, knowledge of average patient values and preferences would be available for every recommendation, the panel members would summarize these values and preferences, and they would be integrated into the recommendations that guideline developers make. The guideline developers asked all chapter chairs before beginning the searches for the relevant literature to identify recommendations that they believed were particularly sensitive to patients' values and preferences. Moderate-quality evidence regarding values and preferences bearing directly on the recommendations proved available for only the chapter that addresses antithrombotic therapy in patients with atrial fibrillation. The panelists bore in mind what average patient values and preferences may be; the process, however, is speculative.

The guideline developer's main strategy for dealing with this unsatisfactory situation is to make the values and preferences underlying the recommendations explicit whenever the panelists believed that value and preference issues were crucial for a recommendation.

In addition, the guideline developers involved three consultants with expertise in the area of values and preferences to collaborate with the chairs of two chapters and try to ensure that the guidelines adequately represented the views of patients. This collaboration led to extensive discussions among the chapter authors and the consultants and the reflection of these discussions in the associated values and preference statements.

## Finalizing and Harmonizing Recommendations

After having completed the steps the guideline developers have described above, the guideline authors formulated draft recommendations before the conference, which laid the foundation for authors to work together and critique the recommendations. Figure 1 in the methodology companion (see "Availability of Companion Documents" field) shows the process of guideline development and review. Drafts of chapters that included draft recommendations were usually distributed for peer review to at least two panel members and were always reviewed by at least one panel editor before the conference. Written critiques were prepared and returned to the authors for revision of their work. At the plenary conference, a representative of each chapter presented potentially controversial issues in their recommendations. Chapter authors met to integrate feedback and consider related recommendations in other chapters and to revise their own guidelines accordingly. Authors continued this process after the conference until they reached agreement within their groups and with other author groups who provided critical feedback. The editors of this supplement harmonized the chapters and resolved remaining disagreements between chapters through facilitated discussion. All major correspondence and discussions at the meeting were recorded in written and audio protocols and are publicly available.

## RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Grading Recommendation			
Grade of Recommendation*	Benefit vs. Risk and Burdens	Methodologic Quality of Supporting Evidence	Implications
Strong recommendation, high-quality evidence, Grade 1A	Desirable effects clearly outweigh undesirable effects, or <i>vice versa</i>	Consistent evidence from RCTs without important limitations or exceptionally strong evidence from observational studies	Recommendation can apply to most patients in most circumstances; further research is very unlikely to change our confidence in the estimate of effect
Strong recommendation, moderate-quality evidence, Grade 1B	Desirable effects clearly outweigh undesirable effects, or <i>vice versa</i>	Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence from observational studies	Recommendation can apply to most patients in most circumstances; higher quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate

Grading Recommendation			
Grade of Recommendation*	Benefit vs. Risk and Burdens	Methodologic Quality of Supporting Evidence	Implications
Strong recommendation, low or very low-quality evidence, Grade 1C	Desirable effects clearly outweigh undesirable effects, or <i>vice versa</i>	Evidence for at least one critical outcome from observational studies, case series, or from RCTs with serious flaws or indirect evidence	Recommendation can apply to most patients in many circumstances; higher-quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate
Weak recommendation, high-quality evidence, Grade 2A	Desirable effects closely balanced with undesirable effects	Consistent evidence from RCTs without important limitations or exceptionally strong evidence from observational studies	The best action may differ depending on circumstances or patient or society values; further research is very unlikely to change our confidence in the estimate of effect
Weak recommendation, moderate-quality evidence, Grade 2B	Desirable effects closely balanced with undesirable effects	Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence from observational studies	Best action may differ depending on circumstances or patient or society values; higher-quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate
Weak recommendation, low or very low-quality evidence, Grade 2C	Desirable effects closely balanced with undesirable effects	Evidence for at least one critical outcome from observational studies, case series, or from RCTs with serious flaws or indirect evidence	Other alternatives may be equally reasonable; higher-quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate

\*The guideline developers use the wording *recommend* for strong (Grade 1) recommendations and *suggest* for weak (Grade 2) recommendations.

## COST ANALYSIS

For these guidelines, the guideline developers implemented recommendations of a recent American College of Chest Physicians (ACCP) task force on integrating resource allocation in clinical practice guidelines by restricting resource expenditure consideration to a small number of recommendations for which they were particularly relevant. The guideline developers relied on two consultants with expertise in economic assessment to help with the process of considering costs in those small numbers of recommendations that we considered very important to the decision.

Recommendations highly sensitive to resource allocation now include value and preference statements regarding how cost issues were integrated.

Refer to "Strategies for incorporating resource allocation and economic considerations" (see "Availability of Companion Documents" field) of the original guideline document for details of the cost analyses.

## **METHOD OF GUIDELINE VALIDATION**

External Peer Review  
Internal Peer Review

## **DESCRIPTION OF METHOD OF GUIDELINE VALIDATION**

The American College of Chest Physicians (ACCP) Health Science Policy (HSP) established a process for the thorough review of all ACCP evidence-based clinical practice guidelines. After final review by the editors, the guidelines underwent review by appropriate NetWorks of the ACCP (for these guidelines, the Cardiovascular and Pulmonary Vascular NetWorks), the HSP, and the Board of Regents. The latter two have the right of approval or disapproval but usually work with the guideline authors and editors to make necessary revisions before final approval. Each group identified primary reviewers who read the full set of chapters as well as individual committee members who were responsible for reviewing one or more chapters. The reviewers considered both content and methodology as well as whether there was balanced, not biased, reporting and adherence to HSP processes. Finally, the *CHEST* editor-in-chief read and forwarded the manuscripts for nonbiased, independent, external peer review before acceptance for publication.

## **RECOMMENDATIONS**

### **MAJOR RECOMMENDATIONS**

The grades of recommendation (1A, 1B, 1C, 2A, 2B, 2C) are defined at the end of the "Major Recommendations" field.

#### **Specific Indications for Antithrombotic Therapy**

#### **Neonatal Deep Vein Thrombosis (DVT): Central Venous Line and Non-Central Venous Line Related**

*In Neonates with Venous Thromboembolism (VTE) (Central Venous Line [CVL] and Non-CVL Related)*

1. The guideline developers suggest that central venous lines (CVLs) or umbilical venous catheters (UVCs) associated with confirmed thrombosis be removed, if possible, after 3 to 5 days of anticoagulation **(Grade 2C)**.
2. The guideline developers suggest either initial anticoagulation, or supportive care with radiologic monitoring **(Grade 2C)**; however, the guideline developers recommend subsequent anticoagulation if extension of the thrombosis occurs during supportive care **(Grade 1B)**.
3. The guideline developers suggest anticoagulation should be with either: (1) Low molecular weight heparin (LMWH) given twice daily (bid) and adjusted to achieve an anti-FXa level of 0.5 to 1.0 U/mL: or (2) UFH for 3 to 5 days adjusted to achieve an anti-FXa of 0.35 to 0.7 U/mL or a corresponding activated partial thromboplastin time (aPTT) range, followed by LMWH. The guideline developers suggest a total duration of anticoagulation of between 6 weeks and 3 months **(Grade 2C)**.
4. The guideline developers suggest that if either a CVL or a UVC is still in place on completion of therapeutic anticoagulation, a prophylactic dose of LMWH be given to prevent recurrent VTE until such time as the CVL or UVC is removed **(Grade 2C)**.
5. The guideline developers recommend against thrombolytic therapy for neonatal VTE unless major vessel occlusion is causing critical compromise of organs or limbs **(Grade 1B)**.
6. The guideline developers suggest that if thrombolysis is required the clinician use tPA and supplement with plasminogen (fresh frozen plasma) prior to commencing therapy **(Grade 2C)**.

**DVT in Children**

*In Children with VTE (CVL and Non-CVL Related): First Thromboembolism (TE) for Children*

1. In children with thrombosis, the guideline developers recommend anticoagulant therapy with either unfractionated heparin (UFH) or LMWH **(Grade 1B)**. (For dosing information see the original guideline document.)
2. The guideline developers recommend initial treatment with UFH or LMWH for at least 5 to 10 days **(Grade 1B)**. For patients in whom clinicians will subsequently prescribe VKAs, the guideline developers recommend beginning oral therapy as early as day 1 and discontinuing UFH/LMWH on day 6 or later than day 6 if the international normalized ratio (INR) has not exceeded 2.0 **(Grade 1B)**. After the initial 5- to 10-day treatment period, the guideline developers suggest LMWH rather than VKA therapy if therapeutic levels are difficult to maintain on VKA therapy or if VKA therapy is challenging for the child and family **(Grade 2C)**.
3. The guideline developers suggest children with idiopathic thromboembolism receive anticoagulant therapy for at least 6 months, using VKAs to achieve a target INR of 2.5 (INR range, 2.0 to 3.0) or alternatively using LMWH to maintain an anti-FXa level of 0.5 to 1.0 U/mL **(Grade 2C)**.

*Underlying values and preferences:* The suggestion to use anticoagulation therapy to treat idiopathic DVTs in children for at least 6 months rather than

on a lifelong basis places a relatively high value on avoiding the inconvenience and bleeding risk associated with antithrombotic therapy, and a relative low value on avoiding the unknown risk of recurrence in the absence of an ongoing risk factor.

4. In children with secondary thrombosis in whom the risk factor has resolved, the guideline developers suggest anticoagulant therapy be administered for at least 3 months using VKAs to achieve a target INR of 2.5 (INR range, 2.0 to 3.0) or alternatively using LMWH to maintain an anti-FXa level of 0.5 to 1.0 U/mL **(Grade 2C)**.
5. In children who have ongoing, but potentially reversible risk factors, such as active nephrotic syndrome or ongoing l-asparaginase therapy, the guideline developers suggest continuing anticoagulant therapy in either therapeutic or prophylactic doses until the risk factor has resolved **(Grade 2C)**.

#### *Recurrent Idiopathic TE for Children*

6. For children with recurrent idiopathic thrombosis, the guideline developers recommend indefinite treatment with VKAs to achieve a target INR of 2.5 (INR range, 2.0 to 3.0) **(Grade 1A)**.

*Remark:* For some patients, long-term LMWH may be preferable; however, there are little or no data about the safety of long-term LMWH in children.

#### *Recurrent Secondary TE for Children*

7. For children with recurrent secondary TE with an existing reversible risk factor for thrombosis, the guideline developers suggest anticoagulation until the removal of the precipitating factor but for a minimum of 3 months **(Grade 2C)**.

#### *In Addition, with Specific Respect to the Management of CVL-related Thrombosis*

8. If a CVL is no longer required, or is nonfunctioning, the guideline developers recommend it be removed **(Grade 1B)**. The guideline developers suggest at least 3 to 5 days of anticoagulation therapy prior to its removal **(Grade 2C)**. If CVL access is required and the CVL is still functioning, the guideline developers suggest that the CVL remain in situ and the patient be anticoagulated **(Grade 2C)**.
9. For children with a first CVL-related DVT, the guideline developers suggest initial management as for secondary thromboembolism as previously described. The guideline developers suggest, after the initial 3 months of therapy, that prophylactic doses of VKAs (INR range 1.5 to 1.9) or LMWH (anti-FXa level range, 0.1 to 0.3) be given until the CVL is removed **(Grade 2C)**. If recurrent thrombosis occurs while the patient is receiving prophylactic therapy, the guideline developers suggest continuing therapeutic doses until the CVL is removed but at least for a minimum of 3 months **(Grade 2C)**.

#### **Use of Thrombolysis in Pediatric Patients with DVT**

In children with DVT, the guideline developers suggest that thrombolysis therapy not be used routinely (**Grade 2C**). If thrombolysis is used, in the presence of physiologic or pathologic deficiencies of plasminogen, the guideline developers suggest supplementation with plasminogen (**Grade 2C**).

### **Thrombectomy and IVC Filter Use in Pediatric Patients with DVT**

1. If life-threatening VTE is present, the guideline developers suggest thrombectomy (**Grade 2C**).
2. The guideline developers suggest, following thrombectomy, anticoagulant therapy be initiated to prevent thrombus reaccumulation (**Grade 2C**).
3. In children > 10 kg body weight with lower-extremity DVT and a contraindication to anticoagulation, the guideline developers suggest placement of a temporary inferior vena cava (IVC) filter (**Grade 2C**).
4. The guideline developers suggest that temporary IVC filters should be removed as soon as possible if thrombosis is not present in the basket of the filter and when the risk of anticoagulation decreases (**Grade 2C**).
5. In children who receive an IVC filter, the guideline developers recommend appropriate anticoagulation for DVT (see the "DVT in Children" section above) as soon as the contraindication to anticoagulation is resolved (**Grade 1B**).

### **Pediatric Cancer Patients with DVT**

#### *Use of Anticoagulants as Therapeutic Agents*

1. In children with cancer, the guideline developers suggest management of VTE follow the general recommendations for management of DVT in children. The guideline developers suggest the use of LMWH in the treatment of VTE for a minimum of 3 months until the precipitating factor has resolved (e.g., use of asparaginase) (**Grade 2C**).

*Remark:* The presence of cancer, and the need for surgery, chemotherapy, or other treatments may modify the risk benefit ratio for treatment of DVT, and clinicians should consider these factors on an individual basis.

#### *Use of Anticoagulant as Thromboprophylaxis*

2. The guideline developers suggest clinicians not use primary antithrombotic prophylaxis in children with cancer and central venous access devices (VADs) (**Grade 2C**).

### **Children with DVT and Antiphospholipid Antibodies (APLAs)**

For children with VTE, in the setting of APLAs, the guideline developers suggest management as per general recommendations for VTE management in children.

*Remark:* Depending on the age of the patient, it may be more appropriate to follow adult guidelines for management of VTE in the setting of APLAs. (See the National Guideline Clearinghouse (NGC) summary of the American College of Chest Physicians [ACCP] chapter [Antithrombotic Therapy for Venous Thromboembolic Disease](#) by Kearon et al.).

## Neonatal RVT

1. For neonates or children with unilateral renal vein thrombosis (RVT) in the absence of renal impairment or extension into the IVC, the guideline developers suggest supportive care with monitoring of the RVT for extension or anticoagulation with UFH/LMWH or LMWH in therapeutic doses; the guideline developers suggest continuation for 3 months **(Grade 2C)**.
2. For unilateral RVT that extends into the IVC, the guideline developers suggest anticoagulation with UFH/LMWH or LMWH for 3 months **(Grade 2C)**.
3. For bilateral RVT with various degrees of renal failure, the guideline developers suggest anticoagulation with UFH and initial thrombolytic therapy with tPA, followed by anticoagulation with UFH/LMWH **(Grade 2C)**.

*Remark:* LMWH therapy requires careful monitoring in the presence of significant renal impairment.

## Primary Antithrombotic Prophylaxis for CVL in Neonates and Children

1. In children with CVLs, the guideline developers recommend against the use of routine systemic thromboprophylaxis **(Grade 1B)**.
2. In children receiving long-term home total parenteral nutrition, the guideline developers suggest thromboprophylaxis with VKAs with a target INR of 2.5 (range 2.0–3.0) **(Grade 2C)**.
3. For blocked CVLs, the guideline developers suggest tPA or recombinant urokinase (UK) to restore patency **(Grade 2C)**. If after at least 30 min following local thrombolytic instillation CVL patency is not restored, the guideline developers suggest a second dose be administered. If the CVL remains blocked following two doses of local thrombolytic agent, the guideline developers suggest investigations to rule out a CVL-related thrombosis be initiated **(Grade 2C)**.

## Primary Prophylaxis for Blalock-Taussig Shunts

For pediatric patients having a modified Blalock-Taussig shunt (MBTS), the guideline developers suggest intraoperative therapy with UFH followed by either aspirin (1–5 mg/kg/d) or no further antithrombotic therapy compared to prolonged LMWH or VKAs **(Grade 2C)**.

## Primary Prophylaxis for Stage 1 Norwoods in Neonates

For patients who underwent the Norwood procedure, the guideline developers suggest UFH immediately after the procedure, with or without ongoing antiplatelet therapy **(Grade 2C)**.

## Primary Prophylaxis for Glenn or Bilateral Cavopulmonary Shunts (BCPS) in Children

In patients who have bilateral cavopulmonary shunts, the guideline developers suggest postoperative UFH **(Grade 2C)**. (For additional information, see Section 1.11 in the original guideline document titled "Primary Prophylaxis for Glenn or Bilateral Cavopulmonary Shunts in Children").

### **Primary Prophylaxis for Fontan Surgery in Children**

For children after Fontan surgery, the guideline developers recommend aspirin (1–5 mg/kg/d) or therapeutic UFH followed by VKAs to achieve a target INR of 2.5 (range, 2.0 to 3.0) **(Grade 1B)**.

*Remark:* The optimal duration of therapy is unknown. Whether patients with fenestrations require more intensive therapy until fenestration closure is unknown.

### **Primary Prophylaxis for Endovascular Stents in Children**

For children having endovascular stents inserted, the guideline developers suggest administration of UFH perioperatively **(Grade 2C)**.

### **Primary Prophylaxis for Dilated Cardiomyopathy in Neonates and Children**

The guideline developers suggest that pediatric patients with cardiomyopathy receive VKAs to achieve a target INR of 2.5 (range, 2.0 to 3.0) no later than their activation on a cardiac transplant waiting list **(Grade 2C)**.

*Underlying values and preferences:* The guideline developer's suggestion for administration of VKAs places a high value on avoiding thrombotic complications, and a relatively low value on avoiding the inconvenience, discomfort and limitations of anticoagulant monitoring, in children who are eligible for transplant, which is a potentially curative therapy.

### **Primary Pulmonary Hypertension**

In children with primary pulmonary hypertension, the guideline developers suggest anticoagulation with VKAs commencing when other medical therapy is commenced **(Grade 2C)**.

### **Biological Prosthetic Heart Valves**

For children with biological prosthetic heart valves, the guideline developers recommend that clinicians follow the relevant recommendations from the adult population (See the NGC summary of the ACCP chapter [Valvular and Structural Heart Disease](#) by Salem et al.)

### **Mechanical Prosthetic Heart Valves**

1. For children with mechanical prosthetic heart valves, the guideline developers recommend that clinicians follow the relevant recommendations from the adult population with respect to the intensity of anticoagulation therapy. (See the NGC summary of the ACCP chapter [Valvular and Structural Heart Disease](#) by Salem et al.)
2. For children with mechanical prosthetic heart valves who have had thrombotic events while on therapeutic antithrombotic therapy or in patients in whom there is a contraindication to full-dose VKAs, the guideline developers suggest adding aspirin therapy **(Grade 2C)**.

## Ventricular Assist Devices (VADs)

1. Following ventricular assist device (VAD) placement, in the absence of bleeding the guideline developers suggest administration of UFH targeted to an anti-factor Xa of 0.35 to 0.7 u/mL **(Grade 2C)**. The guideline developers suggest starting UFH between 8 hours and 48 hours following implantation **(Grade 2C)**.
2. The guideline developers suggest antiplatelet therapy (either aspirin, 1 to 5 mg/kg/d, and/or dipyridamole, 3 to 10 mg/kg/d) to commence within 72 hours of VAD placement **(Grade 2C)**.
3. The guideline developers suggest that once clinically stable, pediatric patients be weaned from UFH to either LMWH (target anti-FXa 0.5–1.0 U/mL) or VKA (target INR, 3.0; range, 2.5–3.5) until transplanted or weaned from VAD **(Grade 2C)**.

## Cardiac Catheterization (CC)

1. For neonates and children requiring CC via an artery, the guideline developers recommend administration of IV UFH prophylaxis **(Grade 1A)**.
2. The guideline developers recommend the use of UFH doses of 100 to 150 U/kg as a bolus **(Grade 1B)**. The guideline developers suggest further doses of UFH rather than no further therapy in prolonged procedures **(Grade 2B)**.
3. The guideline developers recommend against the use of aspirin therapy for prophylaxis for CC **(Grade 1B)**.

## Therapy of Femoral Artery Thrombosis

1. For pediatric patients with a femoral artery thrombosis, the guideline developers recommend therapeutic doses of IV UFH **(Grade 1B)**. The guideline developers suggest treatment for at least 5 to 7 days **(Grade 2C)**.
2. The guideline developers recommend administration of thrombolytic therapy for pediatric patients with limb-threatening or organ-threatening (via proximal extension) femoral artery thrombosis who fail to respond to initial UFH therapy and who have no known contraindications **(Grade 1B)**.
3. For children with femoral artery thrombosis, the guideline developers suggest surgical intervention when there is a contraindication to thrombolytic therapy and organ or limb death is imminent **(Grade 2C)**.
4. The guideline developers suggest that for children in whom thrombolysis or surgery is not required, conversion to LMWH to complete 5 to 7 days of treatment **(Grade 2C)**.

## Peripheral Arterial Catheter Thrombosis in Neonates and Children

1. For pediatric patients with peripheral arterial catheters *in situ*, the guideline developers recommend UFH through the catheter, preferably by continuous infusion (5 U/mL at 1 mL/h) **(Grade 1A)**.
2. For children with a peripheral arterial catheter-related thromboembolism (TE), the guideline developers suggest immediate removal of the catheter **(Grade 1B)**. The guideline developers suggest UFH anticoagulation with or without thrombolysis, or surgical thrombectomy **(Grade 2C)**.

## Neonatal Aortic Thrombosis: UAC Related

1. To maintain umbilical artery catheter (UAC) patency, the guideline developers suggest prophylaxis with a low-dose UFH infusion via the UAC (heparin concentration of 0.25–1 U/mL) **(Grade 2A)**.
2. For neonates with UAC-related thrombosis, the guideline developers suggest therapy with UFH or LMWH for at least 10 days **(Grade 2C)**.
3. For neonates with UAC-related thrombosis, the guideline developers recommend UAC removal **(Grade 1B)**.
4. For neonates with UAC-related thrombosis with potentially life-, limb-, or organ-threatening symptoms, the guideline developers suggest thrombolysis with tPA. When thrombolysis is contraindicated, the guideline developers suggest surgical thrombectomy **(Grade 2C)**.

### **UAC-Related Thrombosis: Effect of Catheter Location**

The guideline developers suggest UACs placement in a high position rather than a low position **(Grade 2B)**.

### **Primary Prophylaxis for Venous Access Related to Hemodialysis**

In patients undergoing hemodialysis, the guideline developers suggest against routine use of VKAs or LMWH for prevention of thrombosis related to central venous lines or fistulas **(Grade 2C)**.

### **Use of UFH or LMWH for Hemodialysis**

The guideline developers suggest the use of UFH or LMWH in hemodialysis **(Grade 2C)**.

### **Kawasaki Disease**

1. In children with Kawasaki disease, the guideline developers recommend aspirin in high doses (80 to 100 mg/kg/d during the acute phase, for up to 14 days) as an anti-inflammatory agent, then in lower doses (1 to 5 mg/kg/d for 6 to 8 weeks) as an antiplatelet agent **(Grade 1B)**.
2. In children with Kawasaki disease, the guideline developers suggest against concomitant use of ibuprofen or other nonsteroidal anti-inflammatory drugs during aspirin therapy **(Grade 2C)**.
3. In children with Kawasaki disease, the guideline developers recommend IV gamma globulin (2 g/kg, single dose) within 10 days of the onset of symptoms **(Grade 1A)**.
4. In children with giant coronary aneurysms following Kawasaki disease, the guideline developers suggest warfarin (target INR, 2.5; INR range, 2.0 to 3.0) in addition to therapy with low-dose aspirin be given as primary thromboprophylaxis **(Grade 2C)**.

### **Neonatal Sinovenous Thrombosis**

1. For neonates with cerebral sinovenous thrombosis (CSVT) without significant intracranial hemorrhage (ICH), the guideline developers suggest anticoagulation, initially with UFH, or LMWH and subsequently with LMWH or VKA for a minimum of 6 weeks, and no longer than 3 months **(Grade 2C)**.

2. For children with cerebral sinovenous thrombosis (CSVT) with significant hemorrhage, the guideline developers suggest radiologic monitoring of the thrombosis at 5 to 7 days and anticoagulation if thrombus propagation is noted **(Grade 2C)**.

### **Childhood CSVT**

1. For children with cerebral sinovenous thrombosis (CSVT), without significant intracranial hemorrhage (ICH), the guideline developers recommend anticoagulation initially with UFH or LMWH and subsequently with LMWH or VKA for a minimum of 3 months relative to no anticoagulation **(Grade 1B)**.
2. The guideline developers suggest that if after 3 months of therapy there is incomplete radiologic recanalisation of CSVT or ongoing symptoms, administration of a further 3 months of anticoagulation **(Grade 2C)**.
3. For children with CSVT with significant hemorrhage, the guideline developers suggest radiologic monitoring of the thrombosis at 5 to 7 days. If thrombus propagation is noted at that time, the guideline developers suggest anticoagulation **(Grade 2C)**.
4. The guideline developers suggest children with CSVT in the context of a potentially recurrent risk factors (e.g., nephrotic syndrome, L-asparaginase therapy) should receive prophylactic anticoagulation at times of risk factor recurrence **(Grade 2C)**.
5. The guideline developers suggest thrombolysis thrombectomy or surgical decompression only in children with severe CSVT in whom there is no improvement with initial UFH therapy **(Grade 2C)**.

### **Neonatal Arterial Ischemic Stroke (AIS)**

1. In the absence of a documented ongoing cardioembolic source, the guideline developers recommend against anticoagulation or aspirin therapy for neonates with a first arterial ischemic stroke (AIS) **(Grade 1B)**.
2. In neonates with recurrent AIS, the guideline developers suggest anticoagulant or aspirin therapy **(Grade 2C)**.

### **Childhood AIS**

1. For children with non-sickle-cell disease-related acute AIS, the guideline developers recommend UFH or LMWH or aspirin (1 to 5 mg/kg/d) as initial therapy until dissection and embolic causes have been excluded **(Grade 1B)**.
2. The guideline developers recommend, once dissection and cardioembolic causes are excluded, daily aspirin prophylaxis (1–5 mg/kg/d) for a minimum of 2 years **(Grade 1B)**.
3. The guideline developers suggest for AIS secondary to dissection or cardioembolic causes, anticoagulant therapy with LMWH or VKAs for at least 6 weeks, with ongoing treatment dependent on radiologic assessment **(Grade 2C)**.
4. The guideline developers recommend against the use of thrombolysis (tPA) for AIS in children, outside of specific research protocols **(Grade 1B)**.
5. The guideline developers recommend for children with sickle-cell disease and AIS, IV hydration and exchange transfusion to reduce sickle hemoglobin levels to at least < 30% total hemoglobin **(Grade 1B)**.

6. For children with sickle-cell disease and AIS, after initial exchange transfusion the guideline developers recommend a long-term transfusion program **(Grade 1B)**.
7. In children with sickle-cell anemia who have transcranial Doppler velocities > 200 cm/s on screening, the guideline developers recommend regular blood transfusion, which should be continued indefinitely **(Grade 1B)**.
8. The guideline developers recommend that children with moyamoya be referred to an appropriate center for consideration of revascularization **(Grade 1B)**.
9. For children receiving aspirin who have recurrent AIS or transient ischemic attacks (TIAs) guideline developers suggest changing to clopidogrel or anticoagulant (LMWH or VKA) therapy **(Grade 2C)**.

### **Purpura Fulminans**

1. For neonates with homozygous protein C deficiency, the guideline developers recommend administration of either 10 to 20 mL/kg of fresh frozen plasma (FFP) every 12 hours (q12h) or protein C concentrate, when available, at 20 to 60 U/kg until the clinical lesions resolve **(Grade 1B)**.
2. The guideline developers suggest long-term treatment with VKAs **(Grade 2C)**, LMWH **(Grade 2C)**, protein C replacement **(Grade 1B)**, or liver transplantation **(Grade 2C)**.

### **Definitions:**

<b>Grading Recommendation</b>			
<b>Grade of Recommendation*</b>	<b>Benefit vs. Risk and Burdens</b>	<b>Methodologic Quality of Supporting Evidence</b>	<b>Implications</b>
Strong recommendation, high-quality evidence, Grade 1A	Desirable effects clearly outweigh undesirable effects, or <i>vice versa</i>	Consistent evidence from RCTs without important limitations or exceptionally strong evidence from observational studies	Recommendation can apply to most patients in most circumstances; further research is very unlikely to change our confidence in the estimate of effect
Strong recommendation, moderate-quality evidence, Grade 1B	Desirable effects clearly outweigh undesirable effects, or <i>vice versa</i>	Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence from observational studies	Recommendation can apply to most patients in most circumstances; higher quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate

Grading Recommendation			
Grade of Recommendation*	Benefit vs. Risk and Burdens	Methodologic Quality of Supporting Evidence	Implications
Strong recommendation, low or very low-quality evidence, Grade 1C	Desirable effects clearly outweigh undesirable effects, or <i>vice versa</i>	Evidence for at least one critical outcome from observational studies, case series, or from RCTs with serious flaws or indirect evidence	Recommendation can apply to most patients in many circumstances; higher-quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate
Weak recommendation, high-quality evidence, Grade 2A	Desirable effects closely balanced with undesirable effects	Consistent evidence from RCTs without important limitations or exceptionally strong evidence from observational studies	The best action may differ depending on circumstances or patient or society values; further research is very unlikely to change our confidence in the estimate of effect
Weak recommendation, moderate-quality evidence, Grade 2B	Desirable effects closely balanced with undesirable effects	Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence from observational studies	Best action may differ depending on circumstances or patient or society values; higher-quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate
Weak recommendation, low or very low-quality evidence, Grade 2C	Desirable effects closely balanced with undesirable effects	Evidence for at least one critical outcome from observational studies, case series, or from RCTs with serious flaws or indirect evidence	Other alternatives may be equally reasonable; higher-quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate

\*The guideline developers use the wording *recommend* for strong (Grade 1) recommendations and *suggest* for weak (Grade 2) recommendations.

## CLINICAL ALGORITHM(S)

None provided

## EVIDENCE SUPPORTING THE RECOMMENDATIONS

### TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations").

## BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

### POTENTIAL BENEFITS

Appropriate monitoring and management of neonates and children receiving antithrombotic therapy

### POTENTIAL HARMS

- *Adverse effects of heparin:* One cohort study reported bleeding in 1.5% (95% confidence interval [CI], 0.0–8.3%) of children treated with unfractionated heparin (UFH) for deep venous thrombosis (DVT)/pulmonary embolus (PE). A more recent study reports a major bleeding rate of 24% in children in pediatric intensive care units receiving UFH.
- *Adverse effects of low molecular weight heparin (LMWH):* Although the risk of major bleeding in neonates remains uncertain, studies have reported the risk of bleeding in neonates as part of larger patient populations. One pilot study reported no bleeding in seven infants < 2 months of age (0%; 95% CI, 0–47%). In a larger series, 4 of 37 infants had major bleeding (10.8%; 95% CI, 3–25.4%). Bleeding occurred locally (at the site of subcutaneous catheters in two newborns with little subcutaneous tissue), and into preexisting abnormalities in the central nervous system (CNS) in a further two newborns. These data suggests that subcutaneous catheters should be used with caution in newborns with little subcutaneous tissue. In a single institution cohort study of 146 courses of therapeutic enoxaparin given to children, major bleeds occurred in 4.8% (95% CI, 2–9.6%) of patients. In a randomized trial (n = 37) of reviparin, major bleeding occurred in 8.1% of patients (95% CI, 1.7–21.9%). There are no data on the frequency of osteoporosis, heparin induced thrombocytopenia (HIT), or other hypersensitivity reactions in children exposed to LMWH.
- *Adverse Effects of vitamin K antagonists (VKAs):* Bleeding is the main complication of VKA therapy. The risk of serious bleeding in children receiving VKAs for mechanical prosthetic valves is < 3.2% per patient-yr (13 case series). In one large cohort (391 warfarin-years, variable target range), the bleeding rate was 0.5% per patient-year.
- *Adverse effects of aspirin:* Neonates may be exposed to aspirin due to maternal ingestion (e.g., treatment for preeclampsia). Clearance of aspirin is slower in neonates, potentially placing them at risk for bleeding for longer periods of time. However, *in vitro* studies have not demonstrated an additive effect of aspirin on the hypofunction of newborn platelets, and evidence linking maternal aspirin ingestion to bleeding in newborns is weak. In neonates, additive antiplatelet effect must be considered if concurrent

- indomethacin therapy is required. In older children, aspirin rarely causes important hemorrhage, except in the presence of an underlying hemostatic defect or in children also treated with anticoagulants or thrombolytic therapy.
- *Adverse Effects of Thrombolytic Therapy:* Thrombolytic therapy has significant bleeding complications in children. Early literature reviews (including 255 patients) reported an incidence of bleeding requiring treatment with packed red blood cells (RBCs) of approximately 20% in pediatric patients. A more recent study reported bleeding in 68% of patients, with bleeding requiring transfusion occurring in 39%.

## CONTRAINDICATIONS

### CONTRAINDICATIONS

- Anticoagulation is contraindicated in active bleeding
- There are well-defined contraindications to thrombolytic therapy in adults. Clinicians should consider similar problems in children as relative but not absolute contraindications to thrombolytic therapy.

## QUALIFYING STATEMENTS

### QUALIFYING STATEMENTS

#### Limitations of These Guideline Development Methods

Limitations of these guidelines include the limited quantity and quality of available studies for some patient groups. Second, it is possible that some authors followed this methodology more closely than others, although the development process was centralized by an evidence-based practice center (EPC) and supervised by the editors. Third, it is possible that the guideline developers missed relevant studies in spite of the comprehensive searching process. Fourth, despite their efforts to begin centralizing the methodologic evaluation of all studies to facilitate uniformity in the validity assessments of the research incorporated into these guidelines, resources were insufficient to conduct this evaluation for all but a few of the recommendations in each chapter. Fifth, the guideline developers performed only few statistical pooling exercises of primary study results. Finally, sparse data on patient preferences and values represent additional limitations inherent to most guideline development methods.

## IMPLEMENTATION OF THE GUIDELINE

### DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy includes local educational programs and tools offered through the American College of Chest Physicians (ACCP) Board of Governors and select other locations. The Veterans Administration (VA) will also participate in a pilot project.

### IMPLEMENTATION TOOLS

## Resources

For information about [availability](#), see the "Availability of Companion Documents" and "Patient Resources" fields below.

## INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

### IOM CARE NEED

Getting Better  
Living with Illness  
Staying Healthy

### IOM DOMAIN

Effectiveness  
Safety

## IDENTIFYING INFORMATION AND AVAILABILITY

### BIBLIOGRAPHIC SOURCE(S)

Monagle P, Chalmers E, Chan A, DeVeber G, Kirkham F, Massicotte P, Michelson AD. Antithrombotic therapy in neonates and children: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008 Jun;133(6 Suppl):887S-968S. [561 references] [PubMed](#)

### ADAPTATION

Not applicable: The guideline was not adapted from another source.

### DATE RELEASED

2001 Jan (revised 2008 Jun)

### GUIDELINE DEVELOPER(S)

American College of Chest Physicians - Medical Specialty Society

### SOURCE(S) OF FUNDING

American College of Chest Physicians

### GUIDELINE COMMITTEE

American College of Chest Physicians (ACCP) Expert Panel on Antithrombotic and Thrombolytic Therapy

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## FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

**Dr. Professor Monagle** discloses that he has received grant monies from the University of Melbourne, the National Health and Medical Research Council of Australia, Roche, and Stago.

**Dr. Chan** reveals no real or potential conflicts of interest or commitment.

**Dr. Massicotte** discloses that she has received grant monies from the Canadian Institutes for Health Research. She has also received consultant fees from Bristol-Myers Squibb, Sanofi-Aventis, Berlin Heart, Boehringer Ingelheim, Bayer, Pfizer, and Azai.

**Dr. Chalmers** reveals no real or potential conflicts of interest or commitment.

**Dr. Michelson** discloses that he has received grant monies from Accumetrics, Arena Pharmaceuticals, Dade Behring, GL Synthesis, Lilly, Daiichi Sankyo, McNeil Consumer Healthcare, Sanofi-Aventis, and Bristol-Myers Squibb. He has also served on an advisory committee for Lilly, Daiichi Sankyo, Sanofi-Aventis, and Bristol-Myers Squibb.

**Dr. deVeber** reveals no real or potential conflicts of interest or commitment.

**Professor Kirkham** reveals no real or potential conflicts of interest or commitment.

## **ENDORSER(S)**

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American Society of Health-System Pharmacists - Professional Association

## **GUIDELINE STATUS**

This is the current release of the guideline.

This guideline updates a previous version: Monagle P, Chan A, Massicotte P, Chalmers E, Michelson AD. Antithrombotic therapy in children: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004 Sep;126(3 Suppl):645S-87S.

## **GUIDELINE AVAILABILITY**

Electronic copies: Available to subscribers of the [Chest - The Cardiopulmonary and Critical Care Journal](#).

Print copies: Available from the American College of Chest Physicians, Products and Registration Division, 3300 Dundee Road, Northbrook IL 60062-2348.

## **AVAILABILITY OF COMPANION DOCUMENTS**

The following are available:

Executive Summary:

- Antithrombotic and thrombolytic therapy executive summary. Chest 2008 Jun; 133:71S-109S.

Background Articles:

- Antithrombotic and thrombolytic therapy. Chest 2008 Jun; 133:110S-112S.
- Methodology for antithrombotic and thrombolytic therapy guideline development. Chest 2008 Jun; 133:113S-122S.
- Grades of recommendation for antithrombotic agents. Chest 2008 Jun; 133:123S-131S.

- Strategies for incorporating resource allocation and economic considerations. Chest 2008 Jun; 133:132S-140S.

Electronic copies: Available to subscribers of the [Chest - The Cardiopulmonary and Critical Care Journal](#).

Print copies: Available from the American College of Chest Physicians, Products and Registration Division, 3300 Dundee Road, Northbrook IL 60062-2348.

## **PATIENT RESOURCES**

None available

## **NGC STATUS**

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